Sustained suppression of Bcr-Abl-driven lymphoid leukemia by microRNA mimics.

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Authors: Jami McLaughlin, Donghui Cheng, Oded Singer, Rita U Lukacs, Caius G Radu, Inder M Verma, Owen N Witte

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Public Summary:
Many cancers and leukemias are associated with strong dominant oncogenic mutations that activate tyrosine kinases and other classes of molecules, including transcription factors and antiapoptotic mechanisms. Some of these events can be targeted with small molecules or antibody-based therapeutics, but many remain intractable. In addition, cancer-related enzyme targets can often mutate, and drug-resistant variants are selected. Therapies directed at the mRNA encoding dominant oncogenes could provide a more global set of technologies for cancer treatment. To test this concept, we have used the model of transformation of hematopoietic cells by the chimeric Bcr-Abl oncogene, a highly activated tyrosine kinase. Our results show that tandem arrays of miRNA mimics, but not single miRNA mimics, directed against the Abl portion of the mRNA and introduced by lentiviral vectors can effectively alter the leukemogenic potency when the degree of suppression of expression of Bcr-Abl is reduced >200-fold from control levels. Only methods capable of such dramatic sustained reduction in the level of expression of highly activated kinase oncogenes are likely to be effective in controlling malignant cell populations.

Scientific Abstract:
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